REVIEW ARTICLE

Eastern Journal of Medicine

East J Med 30(3): 472-478, 2025
DOI: 10.5505/ejm.2025.70104

# Fragile X Syndrome and Infertility: Genetic, Epigenetic, and Clinical Perspectives

**Zeynep Hayırlıoğlu[1*], Zeliha Yücel[2], Emine Berrin Yüksel[3]**

[1]*Department of Histology and Embryology,Health Sciences Institute, Selçuk University, Konya, Turkey*
[2]*Department of Neurology, School of Medicine, Karamanoglu Mehmetbey University, Karaman, Turkey*
[3]*Department of Medical Genetics, School of Medicine, Karamanoglu Mehmetbey University, Karaman, Turkey*

**ABSTRACT**

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and is closely associated with autism spectrum disorder. It results from the expansion of CGG repeats in the *FMR1* gene, leading to hypermethylation and silencing of gene expression, ultimately causing the absence of Fragile X Mental Retardation Protein (FMRP). This protein is essential for synaptic plasticity, neuronal function, and various physiological processes, including reproductive health. While cognitive and behavioral impairments are well-documented, the impact of FXS on reproductive function remains underexplored.

Individuals carrying the full mutation or premutation (55–200 CGG repeats) often experience significant reproductive challenges. Female premutation carriers are at risk of Fragile X-associated primary ovarian insufficiency (FXPOI), leading to infertility and early menopause. Males with FXS frequently exhibit spermatogenic failure, characterized by reduced sperm count and motility due to FMRP deficiency, contributing to infertility. Epigenetic modifications, including DNA methylation and histone alterations, further influence gene expression and clinical variability.

This review explores the genetic and epigenetic mechanisms underlying FXS and their impact on reproductive health. Additionally, current diagnostic and clinical strategies, including genetic counseling, fertility preservation, and assisted reproductive technologies, are discussed. Advancements in gene editing and epigenetic therapies hold promise for mitigating the reproductive effects of FXS. Understanding these mechanisms is crucial for improving clinical management and reproductive outcomes in affected individuals.

**Keywords:** Fragile X Syndrome, *FMR1*, Infertility, FXPOI, Epigenetics, Genetic Counseling, Assisted Reproductive Technologies

## Overview

Fragile X Syndrome (FXS) is the most prevalent inherited cause of intellectual disability and is closely associated with autism spectrum disorder (ASD). It affects approximately 1 in 4,000 males and 1 in 8,000 females, with males experiencing more severe symptoms than females due to the nature of the genetic mutation (1,2). The syndrome is caused by a mutation in the *FMR1* gene located on the X chromosome (3). This mutation results in the expansion of CGG trinucleotide repeats beyond 200 repeats, leading to abnormal methylation of the gene and silencing of its expression (4). This silencing results in the absence of Fragile X Mental Retardation Protein (FMRP), a protein that plays a critical role in neuronal development, synaptic plasticity, and various other physiological processes, including reproductive health (5).

The absence of FMRP profoundly impacts cognitive and behavioral functioning, manifesting as intellectual disabilities, social and emotional challenges, and communication difficulties (5,6). Individuals with FXS may also experience hyperactivity, anxiety, repetitive behaviors, and sensory sensitivities. These manifestations significantly affect their quality of life, social interactions, and educational outcomes (7,8). However, the effects of FXS extend beyond cognitive and behavioral domains, particularly in relation to reproductive health (9–11).

Individuals with FXS, whether they carry the full mutation or the premutation (55-200 CGG repeats), often experience significant reproductive issues. Females with the premutation may develop primary ovarian insufficiency (FXPOI), while both males and females may experience infertility linked to spermatogenic dysfunction and other reproductive system impairments (10,12,13). The

***Corresponding Author:** Zeynep Hayırlıoğlu, Selcuk University, Health Sciences Institute, Department of Histology and Embryology, MSc, E-Mail: zeynepodabashayirlioglu@gmail.com

**ORCID ID: Zeynep Hayırlıoğlu:** 0009-0000-1506-3352, **Zeliha Yücel:** 0000-0002-2303-9704, **Emine Berrin Yüksel:** 0000-0001-7107-1939

**Received:** 13.02.2025, **Accepted:** 04.07.2025

reproductive effects of FXS are often subtle but have profound implications for individuals and families, highlighting the need for specialized clinical management and genetic counseling (14).

This review aims to explore the genetic and epigenetic mechanisms underpinning FXS, focusing on how these mechanisms contribute to infertility and other reproductive health issues. Additionally, it will discuss current clinical strategies for diagnosing and managing FXS, with particular emphasis on infertility prevention, fertility preservation, and assisted reproductive technologies (ART).

## Genetic and Epigenetic Mechanisms in Fragile X Syndrome

**Genetic Basis of Fragile X Syndrome:** FXS is caused by the expansion of CGG repeats in the 5' untranslated region of the *FMR1* gene, located on the X chromosome (15). Normally, the *FMR1* gene contains between 5 and 44 CGG repeats, a number that does not interfere with normal gene expression. However, in individuals with FXS, the number of CGG repeats exceeds 200, leading to the expansion of this sequence (16). This expanded region triggers hypermethylation of the *FMR1* gene's promoter, which prevents the gene from being transcribed into messenger RNA (mRNA) and consequently prevents the synthesis of FMRP (16,17). FMRP is an RNA-binding protein involved in regulating synaptic function, protein synthesis at the synapse, and neuronal development, which are essential for normal cognitive function and synaptic plasticity (17,18).

In individuals with the full mutation (>200 repeats), *FMR1* is silenced, resulting in the complete absence of FMRP. This loss of FMRP leads to cognitive impairments, learning disabilities, and behavioral challenges (16,18). On the other hand, individuals who inherit a premutation (55-200 repeats) do not experience the complete silencing of the gene. Instead, FMRP levels are reduced, which leads to a milder presentation of symptoms (19). However, premutation carriers are at a higher risk of developing other health issues, including FXPOI in females and infertility in both males and females (10,13).

The premutation is associated with the production of toxic RNA molecules. These molecules accumulate within the cells, disrupting normal cellular function and causing RNA toxicity. This toxicity is a significant contributor to the clinical manifestations of FXS, particularly in individuals with the premutation (20,21). Moreover, epigenetic modifications, such as changes in DNA methylation and histone modifications, further regulate *FMR1* gene expression, and these modifications contribute to the severity and variability of symptoms observed in FXS (22).

**Epigenetic Modifications and Their Role in Fragile X Syndrome:** Epigenetic modifications play a critical role in regulating gene expression without altering the DNA sequence itself. These modifications include DNA methylation, histone modifications, and chromatin remodeling, all of which control how genes are turned on or off (22,23). In the case of FXS, the expansion of the CGG repeats leads to hypermethylation of the *FMR1* gene's promoter region, silencing the gene and preventing the synthesis of FMRP (18,24). This epigenetic silencing is a key feature of FXS and is responsible for the cognitive and behavioral symptoms associated with the disorder (22,23).

In addition to the effects of DNA methylation, histone modifications also influence the expression of the *FMR1* gene. Histones are proteins that help package DNA into a compact structure called chromatin (25). Modifications to histones, such as acetylation or methylation, can either activate or repress gene expression by altering the accessibility of the DNA for transcription (26). Studies suggest that these epigenetic modifications may contribute to the variable expression of FXS in individuals with the premutation. For example, some premutation carriers may exhibit partial silencing of the *FMR1* gene due to epigenetic changes in chromatin structure, while others may maintain a higher level of FMRP expression. This variability is thought to be responsible for the wide range of clinical presentations seen in FXS (27,28).

Furthermore, epigenetic changes may also contribute to the severity of reproductive dysfunction in both males and females with FXS. Research suggests that the degree of DNA methylation at the *FMR1* locus may correlate with the severity of ovarian dysfunction in female premutation carriers and with sperm quality in male carriers (14,29). These findings highlight the importance of understanding the epigenetic regulation of the FMR1 gene and its role in reproductive health. Targeting these epigenetic mechanisms could provide new opportunities for developing therapies to mitigate the effects of FXS on fertility and other aspects of health.

## Female Infertility in Fragile X Syndrome

**Primary Ovarian Insufficiency (FXPOI):** One of the most significant reproductive issues in

females with FXS is primary ovarian insufficiency (FXPOI), which affects approximately 20% of women carrying the *FMR1* premutation (12). FXPOI is a condition where the ovaries fail to function properly, leading to irregular menstrual cycles, reduced fertility, and early menopause (13,30). In women with the premutation, FXPOI often presents at an earlier age than in the general population. The pathophysiology of FXPOI in FXS is multifactorial, involving RNA toxicity, abnormal folliculogenesis, and the depletion of ovarian reserve (30,31).

The toxic RNA molecules produced by the expanded CGG repeats interfere with normal follicle development, leading to a reduction in the number of viable oocytes. Additionally, the expansion of the CGG repeats accelerates the depletion of the ovarian follicle pool, resulting in diminished ovarian reserve (31,32). Consequently, women with FXPOI experience early menopause and are at an increased risk of infertility. The clinical features of FXPOI include irregular or absent menstrual cycles, elevated follicle-stimulating hormone (FSH) levels, and reduced levels of anti-Müllerian hormone (AMH), all of which serve as biomarkers of ovarian reserve (22,33).

**Clinical Features and Diagnosis of FXPOI:** The clinical presentation of FXPOI can vary widely among affected women. Some may experience oligomenorrhea (infrequent menstrual cycles) or amenorrhea (complete absence of menstruation) at a young age (29). Elevated FSH levels are often an early indicator of ovarian dysfunction, as the pituitary gland increases FSH production in response to decreased estrogen levels from the ovaries (14,29). Reduced AMH levels are also indicative of diminished ovarian reserve, which is a hallmark of FXPOI (Table 1)(14,29).

The diagnosis of FXPOI in women with FXS is typically confirmed through genetic testing to identify the presence of the *FMR1* premutation, along with hormonal assessments to measure ovarian function. Women who are suspected of having FXPOI should be evaluated for the levels of FSH and AMH in their blood, as well as undergo ultrasound imaging to assess the antral follicle count, which reflects ovarian reserve (34,35).

**Fertility Preservation and Management Strategies:** For women with FXPOI, fertility preservation is an important consideration. Options such as oocyte cryopreservation (egg freezing) allow women to preserve their fertility before ovarian insufficiency becomes severe (36). By freezing eggs at an early age, women with FXPOI can later use their eggs for assisted reproductive technologies (ART) such as in vitro fertilization (IVF) if they experience infertility later in life. However, women with FXPOI have very low ovarian reserve and usually require higher gonadotropin stimulation, resulting in fewer oocytes retrieved compared to unaffected women (37,38).

Hormonal treatments, including the use of birth control pills or hormone replacement therapy (HRT), can help manage the symptoms of ovarian insufficiency and reduce the risk of early menopause (14,39). HRT supports fertility by replacing missing hormones and helps prevent long-term health problems such as osteoporosis, cardiovascular disease, and early menopause symptoms. Maintaining estrogen levels is important in the reproductive system's functionality and general physiological balance. Regular estrogen and progesterone replacement can support ovarian function and promote oocyte development by balancing FSH levels. It can also improve individuals' quality of life by reducing metabolic and bone health problems that may occur due to hormone deficiency(13,39) .

ART, such as IVF and egg donation, are often used in women who experience infertility due to FXPOI. Egg donation can provide women with FXPOI a viable option for having biological children, even if they are unable to conceive with their own eggs (13,36).

In addition to fertility preservation, preimplantation genetic testing (PGT) is available to screen embryos for the FXS mutation. PGT can help prevent the transmission of the *FMR1* mutation to offspring, providing families with the opportunity to have children without passing on the disorder (40).

**Male Infertility in Fragile X Syndrome**

**Spermatogenic Dysfunction and Infertility:** Male infertility is a significant concern in individuals with FXS and premutation carriers. Males with the full mutation of the *FMR1* gene often exhibit spermatogenic failure, which is characterized by the inability to produce viable sperm (41). The fundamental reason for the underlying condition is that FMRP deficiency disrupts cellular growth and division functions. As a result of the disruption in the regulation of cellular development, germ cells undergo apoptosis at an early stage, leading to an increase in tubular spaces with a significant loss of

**Table 1:** Clinical Features of FXPOI in *FMR1* Premutation Carriers

| Feature | Description |
|---|---|
| Menstrual Irregularities | Early menopause, oligomenorrhea, amenorrhea |
| Hormonal Changes | Increased FSH, decreased AMH |
| Ovarian Reserve | Diminished antral follicle count, reduced oocyte quality |
| Reproductive Outcome | Increased risk of infertility, decreased IVF success |

FXPOI: Fragile X-associated primary ovarian insufficiency, *FMR1*: Fragile X Mental Retardation 1

**Table 2:** Molecular Genetic Testing Used in FXS

| Method | Evaluated pathology | Identification rate of cases |
|---|---|---|
| Targeted analysis for pathogenic variants (PCR, Southern blot analysis) | CGG expansion in FMR1 | >99% |
| Methylation analysis | Methylation of FMR1 promoter region | 100% of alleles exhibit this modification. |
| Deletion/duplication analysis | FMR1 deletions/duplications | <1% |
| Sequence analysis | FMR1 sequence variants | <1% |

PCR: Polymerase chain reaction

spermatids and spermatocytes in the seminiferous tubules. These changes in the testicular tissue result in azoospermia or oligozoospermia (10,41). In addition to sperm quality issues, males with FXS typically present with altered hormonal profiles, including elevated FSH and decreased testosterone levels. These hormonal abnormalities contribute to abnormal testicular function and reduced spermatogenesis, which leads to infertility in many males with FXS (42). This results in infertility, often requiring ART to achieve conception.

In premutation-carrier males, the effects on spermatogenesis are milder. Research has demonstrated that disruptions in sperm DNA integrity are often observed, leading to decreased sperm motility and irregularities in the spermatogenesis process, which increase the risk of infertility. Additionally, sperm DNA fragmentation might elevate the risk of transmitting genetic mutations to offspring (29,41).

**Hormonal Profiles and Clinical Management:** In males with FXS, semen analysis is essential for evaluating sperm count, motility, and morphology. Abnormalities in these parameters are commonly seen in individuals with FXS, leading to impaired fertility. Hormonal evaluation, including measurements of testosterone and FSH, can provide further insights into spermatogenic function. In cases of male infertility associated with FXS, ART techniques such as IVF and intracytoplasmic sperm injection (ICSI) are often employed to facilitate fertilization. These techniques allow for the use of a single sperm to fertilize an egg, bypassing the need for normal sperm function (10,43).

Sperm cryopreservation is also an option for men with FXS who wish to preserve their fertility before the onset of infertility. This process involves freezing sperm for future use in ART procedures. Preimplantation genetic testing (PGT) can be utilized to screen embryos for the *FMR1* mutation, ensuring that the disorder is not transmitted to offspring (43).

**Clinical Manifestations and Diagnostic Approaches**

**Genetic Testing and Diagnosis:** In cases of infertility of unknown cause for both males and females, FXS disease and carrier status should be considered. In males with the full mutation, autism spectrum disorder, intellectual disabilities, and accompanying clinical findings such as ataxia or tremor in carriers may assist in diagnosis. However, in women, it may occur together with POI and infertility without showing other clinical findings. The estimated carrier rate of the FMR1 premutation among individuals affected by premature ovarian insufficiency is between 3% and 15% (33). Therefore, FXPOI should be

included in the differential diagnosis for any woman who presents with menopausal symptoms before the age of 40. Additionally, female relatives (mother, sister, aunt) of individuals diagnosed with the FXS full mutation or premutation should be informed about the risks of FXPOI, and genetic counseling should be offered (29).

Genetic testing is essential for the diagnosis of FXS and for identifying premutation carriers. Southern blot analysis and Polymerase chain reaction (PCR) can detect pathogenic CGG expansion and have over 99% diagnostic accuracy. Less than 1% of individuals with FXS have a sequence variant, partial deletion, or complete deletion of *FMR1* (44). If a CGG repeat expansion is not detected but FXS remains suspected, further options like deletion/duplication analysis and sequence analysis should be considered (29) (Table 2). These tests can accurately identify individuals with the full mutation as well as those with the premutation. For women with suspected FXPOI, genetic testing can confirm the presence of the *FMR1* premutation and help guide management decisions (29).

In addition to genetic testing, the measurement of ovarian reserve markers such as AMH and FSH provides important insights into reproductive health. AMH is a key biomarker for ovarian reserve, and low levels of AMH indicate a reduced number of oocytes (11,33). Elevated FSH levels suggest ovarian dysfunction, as the pituitary gland attempts to compensate for the diminished ovarian function (11,33). In males, semen analysis, including sperm count, motility, and morphology, is essential for evaluating fertility status. Hormonal testing, including testosterone and FSH measurements, can further assist in assessing spermatogenic function.

**Genetic Counseling:** Genetic counseling plays a critical role in the management of individuals with FXS or premutation carriers. Counseling helps individuals understand the genetic risks involved in reproduction and the likelihood of passing the mutation on to their offspring. Carriers of the *FMR1* premutation have a 50% chance of passing the mutation to each child, and females have a higher likelihood of having children with FXS due to the expansion of the CGG repeats in subsequent generations (19). Preconceptional counseling can help families make informed decisions regarding reproduction and explore reproductive options such as ART, prenatal testing, and PGT (37,45).

**Therapeutic Approaches for Infertility in FXS**

**Fertility Preservation and ART:** For women with FXPOI, fertility preservation techniques such as oocyte cryopreservation are essential for preserving reproductive potential. These techniques involve freezing eggs before the onset of ovarian insufficiency, allowing women the possibility of conceiving later in life (13,40). Hormonal modulation, including the use of HRT, can help manage the symptoms of ovarian insufficiency and may improve the chances of successful ART.

For men with FXS, sperm cryopreservation is an option for preserving fertility. ART techniques such as ICSI are frequently used to assist men with FXS who have compromised sperm quality. ICSI involves injecting a single sperm directly into an egg, bypassing the need for normal sperm motility. PGT can be employed to screen embryos for the *FMR1* mutation, reducing the risk of passing the disorder to offspring (38).

**Future Directions**

**Advances in Gene Editing and Epigenetic Therapies:** Gene-editing technologies focus on reversing the transcriptional silencing of the *FMR1* gene or reactivating it. Gene-editing technologies, such as CRISPR-Cas9, hold promise for potentially correcting the underlying genetic mutations that cause FXS (46). Research into epigenetic therapies, which aim to reverse the effects of DNA methylation and restore normal gene expression, is an exciting area of investigation (47). A notable aspect in this field is the pharmacological reactivation of the FMR1 gene, achievable through using 5-azadeoxycytidine (5-azadC) and its derivatives. These agents have effectively regulated DNA methylation and histone modification, but their potential clinical use is limited due to their toxic effects (48). Non-coding RNAs appear to be another treatment option. Notably, small, and long noncoding RNAs (lncRNAs), which are involved in DNA methylation and heterochromatinization, are still in development but are believed to hold significant potential for treatment (49). These approaches could offer novel treatments to mitigate the impact of FXS on reproductive health and other aspects of the disorder. As research into these therapies progresses, it is possible that they could lead to new treatment options for individuals with FXS, including those seeking to preserve fertility.

Fragile X Syndrome has far-reaching implications for both cognitive development and reproductive health. The disorder's association with infertility in both males and females underscores the need

for early diagnosis, genetic counseling, and timely intervention. Reproductive options, such as fertility preservation and ART, provide valuable tools for individuals with FXS, while preimplantation genetic testing can help prevent the transmission of the disorder to offspring. As research into the genetic and epigenetic mechanisms of FXS continues to advance, future therapies that target the root causes of infertility and disease progression hold promise for improving the reproductive outcomes and quality of life for affected individuals. Early diagnosis, comprehensive clinical management, and patient-centered care are essential for ensuring the best possible outcomes for individuals with Fragile X Syndrome.

## References


1. Hunter J, Rivero-Arias O, Angelov A, et al. Epidemiology of fragile X syndrome: A systematic review and meta-analysis. Am J Med Genet A. 2014 Jul 3;164(7):1648–58.
2. Turner G, Webb T, Wake S et al. Prevalence of fragile X syndrome. Am J Med Genet. 1996 Jul 12;64(1):196–7.
3. Verkerk AJMH, Pieretti M, Sutcliffe JS et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell. 1991 May;65(5):905–14.
4. Fernandez-Carvajal I, Lopez Posadas B, Pan R et al. Expansion of an FMR1 Grey-Zone Allele to a Full Mutation in Two Generations. The Journal of Molecular Diagnostics. 2009 Jul;11(4):306–10.
5. Garber K, Smith KT, Reines D, Warren ST. Transcription, translation and fragile X syndrome. Curr Opin Genet Dev. 2006 Jun;16(3):270–5.
6. Tassone F, Hagerman RJ, Iklé DN et al. FMRP expression as a potential prognostic indicator in fragile X syndrome. Am J Med Genet. 1999 May 28;84(3):250–61.
7. Berry-Kravis E, Sumis A, Hervey C, Mathur S. Clinic-Based Retrospective Analysis of Psychopharmacology for Behavior in Fragile X Syndrome. Int J Pediatr. 2012;2012:1–11.
8. Davidson M, Sebastian SA, Benitez Y et al. Behavioral Problems in Fragile X Syndrome: A Review of Clinical Management. Cureus. 2022 Feb 2;
9. Reiss S, Zalles L, Gbekie C, Lozano R. Identity and Reproductive Aspects in Females with Fragile X Syndrome. Women's Health Reports. 2021 Nov 1;2(1):500–6.
10. Gu F, Zhang HY, Hu SY et al. Erectile dysfunction in Fragile X patients. Asian J Androl. 2006 Jul;8(4):483–7.
11. Pesso R, Berkenstadt M, Cuckle H et al. Screening for fragile X syndrome in women of reproductive age. Prenat Diagn. 2000 Aug;20(8):611–4.
12. Sherman SL. Premature ovarian failure in the fragile X syndrome. Am J Med Genet. 2000;97(3):189–94.
13. Fink DA, Nelson LM, Pyeritz R et al. Fragile X Associated Primary Ovarian Insufficiency (FXPOI): Case Report and Literature Review. Front Genet. 2018 Nov 27;9.
14. Martin JR, Arici A. Fragile X and reproduction. Curr Opin Obstet Gynecol. 2008 Jun;20(3):216–20.
15. Kremer EJ, Pritchard M, Lynch M et al. Mapping of DNA Instability at the Fragile X to a Trinucleotide Repeat Sequence P(CCG) n. Science (1979). 1991 Jun 21;252(5013):1711–4.
16. Willemsen R, Levenga J, Oostra B. CGG repeat in the FMR1 gene: size matters. Clin Genet. 2011 Sep;80(3):214–25.
17. Santoro MR, Bray SM, Warren ST. Molecular Mechanisms of Fragile X Syndrome: A Twenty-Year Perspective. Annual Review of Pathology: Mechanisms of Disease. 2012 Feb 28;7(1):219–45.
18. Bhakar AL, Dölen G, Bear MF. The Pathophysiology of Fragile X (and What It Teaches Us about Synapses). Annu Rev Neurosci. 2012 Jul 21;35(1):417–43.
19. Nolin SL, Glicksman A, Tortora N et al. Expansions and contractions of the FMR1 CGG repeat in 5,508 transmissions of normal, intermediate, and premutation alleles. Am J Med Genet A. 2019 Jul 2;179(7):1148–56.
20. Galloway JN, Nelson DL. Evidence for RNA-mediated toxicity in the fragile X-associated tremor/ataxia syndrome. Future Neurol. 2009 Nov 1;4(6):785.
21. Tassanakijpanich N, Hagerman RJ, Worachotekamjorn J. Fragile X premutation and associated health conditions: A review. Clin Genet. 2021 Jun 24;99(6):751–60.
22. Warren ST. The Epigenetics of Fragile X Syndrome. Cell Stem Cell. 2007 Nov;1(5):488–9.
23. Kraan CM, Godler DE, Amor DJ. Epigenetics of fragile X syndrome and fragile X-related disorders. Dev Med Child Neurol. 2019 Feb 7;61(2):121–7.
24. Valor LM, Morales JC, Hervás-Corpión I, Marín R. Molecular Pathogenesis and Peripheral Monitoring of Adult Fragile X-Associated Syndromes. Int J Mol Sci. 2021 Aug 4;22(16):8368.

25. Mariño-Ramírez L, Kann MG, Shoemaker BA, Landsman D. Histone structure and nucleosome stability. Expert Rev Proteomics. 2005 Oct 9;2(5):719–29.
26. Zhang Y, Sun Z, Jia J, Du T et al. Overview of Histone Modification. In 2021. p. 1–16.
27. Coffee B, Zhang F, Ceman S, Warren ST, Reines D. Histone Modifications Depict an Aberrantly Heterochromatinized FMR1 Gene in Fragile X Syndrome. The American Journal of Human Genetics. 2002 Oct;71(4):923–32.
28. Kumari D, Usdin K. The distribution of repressive histone modifications on silenced FMR1 alleles provides clues to the mechanism of gene silencing in fragile X syndrome. Hum Mol Genet. 2010 Dec 1;19(23):4634–42.
29. Ezzell Hunter J, Berry-Kravis E, Hipp H, Todd PK. FMR1 Disorders. 1998.
30. Bretherick KL, Fluker MR, Robinson WP. FMR1 repeat sizes in the gray zone and high end of the normal range are associated with premature ovarian failure. Hum Genet. 2005 Aug 2;117(4):376–82.
31. Wittenberger MD, Hagerman RJ, Sherman SL et al. The FMR1 premutation and reproduction. Fertil Steril. 2007 Mar;87(3):456–65.
32. Allen EG, Sullivan AK, Marcus M et al. Examination of reproductive aging milestones among women who carry the FMR1premutation. Human Reproduction. 2007 Aug 1;22(8):2142–52.
33. Pastore LM, Johnson J. The FMR1 gene, infertility, and reproductive decision-making: A review. Vol. 5, Frontiers in Genetics. Frontiers Research Foundation; 2014.
34. Fink DA, Nelson LM, Pyeritz R et al. Fragile X Associated Primary Ovarian Insufficiency (FXPOI): Case Report and Literature Review. Vol. 9, Frontiers in Genetics. Frontiers Media S.A.; 2018.
35. Nelson LM. Primary Ovarian Insufficiency. New England Journal of Medicine. 2009 Feb 5;360(6):606–14.
36. The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013 Jan;99(1):37–43.
37. Avraham S, Almog B, Reches A et al. The ovarian response in fragile X patients and premutation carriers undergoing IVF–PGD: reappraisal. Human Reproduction. 2017 Jul;32(7):1508–11.
38. Fernández RM, Peciña A, Lozano-Arana MD et al. Clinical and Technical Overview of Preimplantation Genetic Diagnosis for Fragile X Syndrome: Experience at the University Hospital Virgen del Rocio in Spain. Biomed Res Int. 2015;2015:1–6.
39. Hipp HS, Charen KH, Spencer JB, Allen EG, Sherman SL. Reproductive and gynecologic care of women with fragile X primary ovarian insufficiency (FXPOI). Menopause. 2016 Sep;23(9):993–9.
40. Ishizuka B. Current Understanding of the Etiology, Symptomatology, and Treatment Options in Premature Ovarian Insufficiency (POI). Front Endocrinol (Lausanne). 2021 Feb 25;12.
41. Reyniers E, Vits L, De Boulle K et al. The full mutation in the FMR–1 gene of male fragile X patients is absent in their sperm. Nat Genet. 1993 Jun;4(2):143–6.
42. Johannisson R, Rehder H, Wendt V, Schwinger E. Spermatogenesis in two patients with the fragile X syndrome. Hum Genet. 1987 Jun;76(2):141–7.
43. Black LD, Godart ES, Turek PJ, Ryan IP. Fertility Preservation for Genetic Indication. Curr Genet Med Rep. 2020 Sep 27;8(3):93–100.
44. Sitzmann AF, Hagelstrom RT, Tassone F, Hagerman RJ, Butler MG. Rare FMR1 gene mutations causing fragile X syndrome: A review. Am J Med Genet A. 2018 Jan 27;176(1):11–8.
45. Burlet P, Frydman N, Gigarel N et al. Multiple displacement amplification improves PGD for fragile X syndrome. MHR: Basic science of reproductive medicine. 2006 Oct 1;12(10):647–52.
46. Yrigollen C, Davidson B. CRISPR to the Rescue: Advances in Gene Editing for the FMR1 Gene. Brain Sci. 2019 Jan 21;9(1):17.
47. Nobile V, Pucci C, Chiurazzi P, Neri G, Tabolacci E. DNA Methylation, Mechanisms of FMR1 Inactivation and Therapeutic Perspectives for Fragile X Syndrome. Biomolecules. 2021 Feb 16;11(2):296.
48. Tabolacci E, Palumbo F, Nobile V, Neri G. Transcriptional Reactivation of the FMR1 Gene. A Possible Approach to the Treatment of the Fragile X Syndrome. Genes (Basel). 2016 Aug 17;7(8):49.
49. Shitik EM, Velmiskina AA, Dolskiy AA, Yudkin D V. Reactivation of FMR1 gene expression is a promising strategy for fragile X syndrome therapy. Gene Ther. 2020 Jun 12;27(6):247–53.